UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/403,539	10/22/99	DEAN	

HM12/0828

PAUL K LEGAARD
WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS
ONE LIBERTY PLACE 46TH FLOOR
PHILADELPHIA PA 19103

EXAMINER	
SHIBUYA, M	

ART UNIT	PAPER NUMBER
1635	15

DATE MAILED: 08/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary	Application No. 09/403,539	Applicant(s) DEAN ET AL.
	Examiner Mark L. Shibuya	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 18, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *27-29 and 31-33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-29, 32, and 33* is/are rejected.

7) ☒ Claim(s) *31* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/7/01 has been entered.

2. Claims 27-29 and 31-33 are pending.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed 4/30/01 in Paper No. 10, is a duplicate of the IDS filed 4/24/00 in Paper No. 5. The examiner thanks the applicant for generously providing new copies of the lost references. Therefore, the IDS has been fully considered. Another copy of the IDS filed 4/24/00 in Paper No. 5, now fully initialed, is attached to the instant Office action.

Claim Objections

4. Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 31 is drawn to the method of claim 27, wherein the oligonucleotide comprises a 2'-O-alkyl or 2'-O-alkoxyalkoxy modification; however claim 27 was amended in the response to the previous Office action to contain a limitation that the

oligonucleotide comprise a 2'-O-alkyl or 2'-O-alkoxyalkoxy modification. Therefore claim 31 fails to further limit newly amended claim 27, from which claim 31 depends.

Double Patenting

5. Claims 27, 28, 31, 32, and 33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 34 of copending Application No. 08/847,151. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed methods of the instant application drawn to modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide that hybridizes to said target nucleic acid; wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification, wherein said 2'-O-alkyl modification is a 2'-O-methyl or 2'-O-propyl modification, and wherein said 2'-alkoxyalkoxy modification is a 2'-methoxyethoxy modification, **encompasses** the claimed method of copending Application No.08/847,151, drawn to modulating expression of a target nucleic acid comprising administering into the alimentary canal, an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid, and which has enhanced bioavailability compared to a phosphorothioate oligonucleotide; wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification, wherein said 2'-O-alkyl modification is a 2'-O-methyl or 2'-O-propyl modification, and wherein said 2'-alkoxyalkoxy modification is a 2'-methoxyethoxy modification.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claim 29 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 34 of copending Application No. 08/847,151, in view of Milligan.

a. Claim 29 of the instant application is drawn to methods for modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid, wherein said nitrogenous, heteroatomic backbone modification is a methylene(methylimino) modification and wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification.

b. Claim 34 of copending Application No. 08/847,151 is drawn to methods for modulating expression of a target nucleic acid comprising administering into the alimentary canal, an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid, wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification, and which has enhanced bioavailability compared to a phosphorothioate oligonucleotide.

c. Milligan et al., *Current Concepts in Antisense Drug Design*, J. Medicinal Chemistry 36 (14) 1923 (1993), at p. 1923, Table 1 and p. 1931, Figure 3 teach oligonucleotides comprising a heteroatomic backbone modification that is a methylene(methylimino) modification.

d. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used methods for modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide that has at least one nitrogenous heteroatomic backbone modification and hybridizes to said target nucleic acid and wherein said nitrogenous, wherein the heteroatomic backbone modification is a methylene(methylimino) modification and wherein the oligonucleotide has a 2'-O-alkyl or 2'-alkoxyalkoxy modification. One of ordinary skill in the art would have been motivated to use a heteroatomic backbone modification that is a methylene(methylimino) modification because the reference of Milligan et al., at pp. 1931-33, teaches that heteroatomic backbone modifications that are methylene(methylimino) modifications will increase the stability and cellular uptake of antisense oligonucleotides.

This is a provisional obviousness-type double patenting rejection.

7. ***Claim Rejections - 35 U.S.C. § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 27, 28, 31, 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al.

a. Claims 27, 28, 31, 32 are drawn to methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide comprising a 2'-O-alkyl or 2'-O-alkoxyalkoxy modification.

b. Agrawal et al., Biochemical Pharmacology 50 (4), 571-576 (1995), throughout the publication, and especially at p. 571, para 2, 572, para 3 teach methods of enhancing bioavailability of an oligonucleotide during or after administration of said oligonucleotide into the alimentary canal, comprising replacing at least one sugar moiety of the oligonucleotide with a 2-O-methyloligoribonucleotide sugar moiety which contains a modification at the 2' position that is a 2-O-alkyl modification; wherein said 2'-O-alkyl modification is a 2-O-methyl modification; wherein said administration into the alimentary canal is oral, sublingual or buccal administration.

10. Claims 27, 28, 31, 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Simon et al., U.S. Patent No. 6,005,094

a. Claims 27, 28, 31, 32 are drawn to methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide comprising a 2'-O-alkyl or 2'-O-alkoxyalkoxy modification.

b. Simon et al., U.S. Patent No. 6,005,094, throughout the patent and especially at col. 1, lines 18-53, col. 2, lines 5-15 and lines 36-42, col. 4, lines 15-25, col. 6, lines 9-67, col. 7, lines 1-

53, teach methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide that has a 2'-O-alkyl modification that is an 2'-O-methyl or a 2'-O-propyl modification and a heteroatomic backbone modification that is methylphosphonate. Simon et al. teach modification of the 2' position on the sugar moiety of the nucleosides in order to avoid depurination due to the acidic conditions of the stomach.

11. Claims 27, 28, 31, 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Arnold, Jr. et al., U.S. Patent 5,792,615.

a. Claims 27, 28, 31, 32 are drawn to methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an oligonucleotide comprising a 2'-O-alkyl or 2'-O-alkoxyalkoxy modification.

b. Arnold, Jr. et al., U.S. Patent 5,792,615, throughout the patent and especially at col. 5, lines 29-38, col. 9, lines 31-34, col. 26, line 47-col. 27, line 11, disclose mixed oligomers having internucleoside modifications, including phosphorothioate internucleoside linkages, and 2'-O-methyl nucleosides, wherein the internucleoside modifications increase oligonucleotide stability and wherein oligomers comprising 2'-O-methyl and 2'-O-alkyl nucleosides resist the acidic conditions of the stomach and so are particularly suited for oral administration.

Claim Rejections - 35 U.S.C. § 103

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 27-29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Simon et al., U.S. Patent No. 6,005,094, Arnold, Jr. et al., U.S. Patent 5,792,615, and Agrawal et al., Biochemical Pharmacology 50 (4), 571-576 (1995), each taken separately and each further in view of Hanecak et al., Vlassov et al., and Milligan et al.

a. Claims 28-30, 32 and 33 are drawn to modulating gene expression comprising administering into the alimentary canal in an oral, rectal, endoscopic, sublingual or buccal manner, a modified oligonucleotide that has enhanced bioavailability compared to a phosphorothioate oligonucleotide of the same sequence, said modified oligonucleotide comprising at least one nitrogenous heteroatomic backbone modification, and variations thereof.

b. **Simon et al., U.S. Patent No. 6,005,094**, throughout the patent and especially at col. 1, lines 18-53, col. 2, lines 5-15 and lines 36-42, col. 4, lines 15-25, col. 6, lines 9-67, col. 7, lines 1-53, teach methods of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide that has a 2'-O-alkyl modification that is an 2'-O-methyl or a 2'-O-propyl modification and a heteroatomic backbone modification that is methylphosphonate. Simon et al. teach modification of the 2' position on the sugar moiety of the nucleosides in order to avoid depurination due to the acidic conditions of the stomach. Simon et al. teach phosphorothioate heteroatomic backbone modifications.

c. **Arnold, Jr. et al.**, U.S. Patent 5,792,615, throughout the patent and especially at col. 5, lines 29-38, col. 9, lines 31-34, col. 26, line 47-col. 27, line 11, disclose mixed oligomers having internucleoside modifications, including phosphorothioate internucleoside linkages, and 2'-

O-methyl nucleosides, wherein the internucleoside modifications increase oligonucleotide stability and wherein oligomers comprising 2'-O-methyl and 2'-O-alkyl nucleosides resist the acidic conditions of the stomach and so are particularly suited for oral administration.

d. **Agrawal et al.**, Biochemical Pharmacology 50 (4), 571-576 (1995), throughout the publication, and especially at p. 571, para 2, 572, para 3 teach methods of enhancing bioavailability of an oligonucleotide during or after administration of said oligonucleotide into the alimentary canal, comprising replacing at least one sugar moiety of the oligonucleotide with a 2-O-methyloligoribonucleotide sugar moiety which contains a modification at the 2' position that is a 2-O-alkyl modification; wherein said 2'-O-alkyl modification is a 2-O-methyl modification; wherein said administration into the alimentary canal is oral, sublingual or buccal administration.

e. None of the references of Simon et al., Arnold et al., or Agrawal et al. teaches oligonucleotides comprising a 2'-alkoxyalkoxy modification that is a 2'-methoxyethoxy modification or methylene(methylimino); or rectal administration of oligonucleotides.

f. **Hanecak et al.** (Journal Of Virology, Aug. 1996, Vol. 70, No. 8, pp. 5203-5212), at p. 5204, para 3, 5208, para 1, teach oligonucleotides comprising 2'-alkoxyalkoxy modifications that are 2'-methoxyethoxy modifications in order to increase nuclease resistance and hybridization affinity. Hanecak et al. teach heteroatomic backbone modifications that are phosphorothioate modifications.

g. **Vlassov et al.**, *Penetration of oligonucleotides into mouse organism through mucosa and skin*, FEBS Letters 327 (3), 271-274 (1993), throughout the publication and especially at p.

271, para 2, 3 and p. 272, para 1, and the abstract, teach methods comprising an oligonucleotide which, during or after administration into the alimentary canal, has bioavailability; wherein said administration into the alimentary canal is oral, rectal, sublingual, or buccal administration for therapeutic benefit; and modulating gene expression comprising administering into the alimentary canal an effective amount of an oligonucleotide which, during or after administration into the alimentary canal, has bioavailability.

h. **Milligan et al.** (Journal of Medicinal Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-1937), at p. 1923, Table 1 and p. 1931, para 2, Figure 3, and p. 1932, para 5 to 1933, para 1, teach modified oligonucleotides comprising at least one nitrogenous heteroatomic backbone modification, including methylene(methylimino) linkages, in order to impart stability and enhance affinity and cellular permeation. Milligan et al. teach heteroatomic backbone modifications that are phosphorothioate modifications.

i. It would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art to use methods for modulating gene expression comprising administering into the alimentary canal in an oral, rectal, endoscopic, sublingual or buccal manner, a modified oligonucleotide comprising a nitrogenous heteroatomic backbone modification that was a methylene(methylimino) modification or a 2'-O-alkoxyalkoxy modification that was a 2'-methoxyethoxy modification, and variations thereof, including rectal administration.

j. One of ordinary skill in the art would have been motivated to use a 2'-alkoxyalkoxy modifications that was a 2'-methoxyethoxy modification, because Simon et al., Arnold et al., and

Agrawal et al. teach the alkylation of the 2' position of the nucleoside sugar moiety to avoid depurination in the highly acid environment of the stomach and because Hanecak et al. teach a 2'-alkoxyalkoxy modification that was a 2'-methoxyethoxy modification in order to increase nuclease resistance and hybridization affinity. One of ordinary skill in the art would have been motivated to use a modified oligonucleotides comprising a methylene(methylimino) linkages, in order to impart stability and enhance affinity and cellular permeation, as taught by Milligan et al. One of ordinary skill in the art would have been motivated to administer oligonucleotides by rectal, sublingual, or buccal administration, because Vlassov et al., teach these routes of administration to be of therapeutic value.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mark L. Shibuya (SRC),* whose telephone number is (703) 308-9355, and/or to the patent analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.
15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.
16. Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.

Mark L. Shibuya
Patent Examiner
Technology Center 1600
August 24, 2001
17.